UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,640	03/01/2004	Michael D. West	60141.0022USU2	9766

28120 7590 06/05/2009

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
06/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/790,640	WEST ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-12,14-16,21-25,27-36 and 106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-12,14-16,21-25,27-36 and 106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/18/2009 has been entered.

Claims 1,6,7, 14,21-25,27,29,28 are amended. Claims 2,9,13,17-20,26 and 37-105 have been cancelled. Claim 106 is added. Claims 1,3-8,10-12,14-16,21-25,27-36 and 106 are pending and under consideration in the instant office action.

The instant application is a continuation of USSN 09/527,026, now abandoned.

Claim Objections

Claim 16 is objected to because of the following informalities: Claim 16 depends from a cancelled claim. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claim 1 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4-6 of U.S. Patent No. 6,808,704 is withdrawn in light of Applicant's arguments.

Claims 1,3-8,10-12,14-16,21-24,29-36, as amended, remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 87-92,94-117 of copending Application No. 11/079,930. Although the conflicting claims are not identical, they are not patentably distinct from each other because while the claims of '930 are not specifically drawn to mammals, the instant claimed methods utilizing reprogramming of somatic cell nuclei by nuclear transfer were notably used in mammalian species. Thus, the generic claimed "cell" in '930 renders obvious the instant claimed mammalian cell..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has requested that this rejection be held in abeyance until otherwise allowable subject matter is identified, at which time, the filing of a TD will be considered.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1) Claims 1,3-8,10-12,14-16 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method using fetal fibroblast donor cells, does not reasonably provide enablement for the claimed method using any donor cell. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are drawn to a method of nuclear transfer using a near senescent or senescent donor cell of any type to form a blastocyst, isolation of a whole or part of the developing blastocyst, formation of a teratoma with said blastocyst whole or part, and isolation of a cell from the teratoma to obtain a cell with increased remaining populations compared to the donor.

The specification teaches carrying out the claimed method using a fetal fibroblast wherein the resulting cell has increased telomere length. The increased telomere length was an unexpected and novel finding as the earlier Dolly cloning using mammary epithelial cells was found to result in cell with shortened telomeres. Post-filing, Lanza reported the lengthening of telomeres in cells resulting from nuclear transfer in **Science** (2000, 288:665-669). Lanza explains that the apparent discrepancy in the

length of the telomeres in cloned cells may be due to cell type used (see page 668, col. 3). Fetal fibroblasts express telomerase whereas adult somatic cells do not (Ulaner, 1997, **Molecular Reproduction,** 3:769-773, see page 769). Thus, absent evidence to the contrary, it appears that at the time of filing the art taught only lengthening of telomeres and otherwise 'rejuvenation' of the cells occurred only when nearly senescent fetal fibroblasts were used.

2) Claims 7,14,21-25,27-36 and 106 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods 1) not requiring any genetic alteration requiring homologous recombination and 2) for developing a mammal by transfer of and embryo into a female host, and 3) for random genetic modifications using fibroblasts as donors does not reasonably provide enablement for 1) performing homologous recombination using a near senescent cell or 2) developing a mammal by transferring an ES cell alone into a female host 3) or for genetic modification in culture of any donor cell other than a fibroblast. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence

or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are overly broad in two respects. The claims are drawn to standard nuclear transfer techniques with two differences. First, the claims require use of senescent or near senescent cells. Second, the claims involve genetic modification of donor cells. The claims encompass use of transgenic or genetically modified donor mammals as a source of the donor cell, to which no in vitro genetic modification would be necessary to meet the limitations of the claims (for example, claims 7 and 25). The claims also encompass isolating a donor cell from a mammal and genetically modifying it in vitro. Genetic modification encompasses homologous recombination to achieve targeted gene insertions, deletions or alterations. The claims require doing so in a senescent or near senescent cell. The specification teaches use of sensescent or near-senescent adult and fetal fibroblast cells, i.e. they have completed 90-95% of their lifespan with less than 2-3 population doublings remaining, in nuclear transfer. The specification does not teach effecting any genetic modification in the donor cells.

The state of the art at the time of filing held that no primary cell had a sufficient number of population doublings left in their life span to perform homologous recombination followed by nuclear transfer. Additionally, only fetal fibroblasts had been genetically modified at all, i.e. random transgene insertion, with enough lifespan left for effective nuclear transfer (see Schnieke, 1997, **Science**, 278:2130-2133; Cibelli, 1998, **Science**, 280:1256-1258, specifically, page 1256, col. 2, paragraph 1). Denning taught that primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence [**Cloning and Stem Cells**, 3:221-231, 2001, specifically refer to page 222, col. 1, lines 5-8] [see also, Clark, **Transgenic Research**, 2000, 9:263-275]. In a study of sheep and goat primary somatic cells, Denning found that of primary somatic cells,

fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. Sheep primary cell cultures primarily were composed of fibroblasts after the third passage or about 12 doublings (Denning, page 224, col. 2, lines 11-13). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (Denning, page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Additional studies of cell cultures prepared from fetal pig organs (gut, kidney, lung and mesonephros) showed that these cells senesced or entered crisis after even fewer doublings than the fibroblast cultures (page 225, col. 1-2, bridg. sent.). The art further taught at the time of filing, that the even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for nuclear transfer, meaning that targeting frequency was lower than expected (page 228, col. 1-2, bridg. sent.). Similar experiments in pigs demonstrated that all the clones senesced, and no targeted cells for nuclear transfer were obtained. Therefore, the claims are not enabled so far as they require genetic modification in culture that is demonstrated by the art to drive the cells to a senescent state to the extent that they are no longer effective in completing the nuclear transfer process.

The claims also require generating a newborn mammal using a naked ES that has not been introduced into a blastocyst (see claim 25, steps c-d, for example. The only manner in which an ES cell can give rise to an animal is for its nucleus to be transferred to an enucleated oocyte, which is one aspect of the claims, or for the ES cell to be placed in a blastocyst where it contribute to make a chimeric embryo.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7,14 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

The rejection of claim 1 is withdrawn in light of Applicant's amendment to the claim.

Claims 7 and 14 remain vague and unclear and newly added claim 106 is unclear because the nature of the alteration of the genome is not adequately described. Applicant has clarified the claim. However, the newly added phrase "at least one native gene of said mammalian primary cell is disrupted" remains vague. It is not clear if this, like the transfection of a heterologous gene, is intended to occur using recombinant methods or if a randomly occurring mutation or other genetic alteration is intended.

The rejection of claim 13 is rendered moot by the cancellation of the claim.

Claim 25 remains confusing and unclear. Applicant has amended the claim to read "a primary mammalian cell that has been genetically altered". However, there is not baseline for determining the alteration. The alteration could be a result of DNA methylation, changes in DNA conformation, insertions, deletions, mismatches. Some of these require active, intentional genomic alterations after isolation of the primary cell. Others, are descriptive of any cell prior to isolation. Thus, it is not clear what is encomapssed by the claim.

The rejection of claim 84 is rendered moot by the cancellation of the claim.

Claim 25, as amended is further unclear in reference to "the cell" throughout the claim. For example, at line 8, step (b), and step (e), it is not clear what "the cell is". It is not clear if it is referring the nuclear transfer unit formed in step (a) or a cell resulting from the developing NT unit. The claim is further unclear in referring to "the cell resulting from the nuclear transfer" as multiple rounds of nuclear transfer are encompassed by the claim. Additionally, the claim appears to have no beginning step. The claim starts "between genetic manipulations…" , rendering it unclear how the claim is to start and with what cell the claim is to start with.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371 (c) of this title before the invention thereof by the applicant for patent.

The rejection of claims 21 and 25-28 under 35 U.S.C. 102(a) and (e) as being anticipated by Strelchenko et al. (US Patent 6,011,197) or Damiani et al. (US Patent 6,258,998) is *withdrawn*. The rejection is moot with respect to claims 39-39,69-78,80-92 and 94-105 as the claims have been cancelled.

The rejection of claims 21,25-28,37-39,69-78,80-92 and 94-105 under 35 U.S.C. 102(b) as being anticipated by Robl et al. (WO 98/07841) as evidenced by Evans et al. (Nature Genetics 23:90-93, 1999) is *withdrawn*.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632